

REMARKS

Claims 1-28 and 33-38 are pending in the subject application. Applicants have not amended, added or canceled any claims by this response.

Rejections Under 35 U.S.C. §102(e)

In the September 10, 2004 Final Office Action the Examiner rejected Claims 1-4, 6, 12, 13, 21-23, 33, 34 and 36-38 under 35 U.S.C. 102(e) as allegedly anticipated by Schultz et al., US 6,180,415 ("the '415 patent").

The Examiner alleged that the '415 patent discloses a method for detecting the presence of and information about a target having a molecular feature of interest (col 5 and 6, col 34, line 6 - col 35 line 33). The Examiner alleged that the '415 patent discloses contacting the target with one or more plasmon resonant particles ("PRE's" or "PRP's") (which the Examiner characterized as labels) having surface localized molecules to produce an interaction between the molecular feature and the localized molecules. The Examiner alleged that the '415 patent discloses that the PRE's can accept pulses between 5 to 500 femtosecond for driving second harmonic generation processes. Further, the Examiner alleged that with respect to second harmonic active-label as recited in the instant claims in the specification on page 2, lines 19-23 the applicant defines that second harmonic active-labels are second harmonic-active moieties which can be attached to a molecule of interest that is not second harmonic active and applicant further defines (page 8, lines 6-11) that a second harmonic refers to a frequency of light that is twice the frequency of a fundamental beam of light and that a second harmonic-active moiety is a substance which when irradiated with a fundamental beam of light generates a second harmonic of the fundamental. The Examiner

alleged that the '415 patent discloses that the PRE's (labels) can accept pulses between 5 to 500 femtosecond for driving second harmonic generation. On this basis the Examiner alleged that the '415 patent discloses second harmonic labels and thus the '415 patent discloses the same label as recited in the claims and that the labels would be hyperpolarizable and contribute to a net orientation at the interface.

In response, applicants note that the Examiner's basis for the rejection is the premise that disclosure of a particle which may be capable of accepting energy pulses employed in a certain process teaches that certain process. Applicants respectfully disagree.

Initially, applicants note that second harmonic generation is a facultative process. Salafsky et al. in J. Phys. Chem. B 2000 104:7752-7755 (right column of page 7752), submitted in the Information Disclosure Statement filed July 10, 2001, explains that for a particle to be a second harmonic-active label it must be (1) noncentrosymmetric, and it (2) must be made to adopt a net orientation (3) at the (investigated) interface.

NONCENTROSYMMETRY IS REQUIRED

While the '415 patent asserts certain particles are capable of accepting "5-500 femtosecond pulses", the '415 patent does not disclose how to use such particles as second harmonic-active labels. In fact, the '415 patent does not distinguish between the properties of spherical and non-spherical particles that are capable of accepting "5-500 femtosecond pulses" with respect to the particles' second harmonic activity. Applicants teach that spherical particles are centrosymmetric and hence not second harmonic-active. The '415 patent makes no such distinction between spherical and non-spherical particles because the '415

patent is not teaching a method of using second harmonic-active labels, like applicants claim. Clearly, a mere teaching that a particle is capable of accepting short duration pulses is not a teaching of a method of using such particles as second harmonic-active labels. Accordingly, the '415 patent fails to teach how to practice a method which requires particles to be second harmonic-active labels.

HYPERPOLARIZABILITY IS REQUIRED

Furthermore, with respect to hyperpolarizability, Levine et al. (1976) J. Phys. Chem. 65(6): p2429, **Exhibit A** annexed hereto, teaches that hyperpolarizability vanishes in centrosymmetric entities. Accordingly, the spherical (i.e. centrosymmetric) particles discussed by the '415 patent (e.g. see col. 9, lines 66 to 67), while capable of accepting 5-500 femtosecond pulses, are not hyperpolarizable. Applicants, on the other hand, require their labels to be hyperpolarizable. Thus, the '415 patent further fails to teach use of its particles as second harmonic-active labels because the '415 patent fails to distinguish between, and teach the properties of, hyperpolarizable and non-hyperpolarizable particles.

In short, the statement in the '415 patent that its particles can accept the pulses means merely what it says, i.e. the particles can accept the pulses, and not that they are second harmonic-active. The position taken that mere capability of accepting the pulses endows the particles as second-harmonic active would mean that the '415 patent teaches centrosymmetric second harmonic-active labels, i.e. violating the requirements for actual second harmonic generation. Therefore the contention that "thus the '415 patent discloses the same label as recited in the claims", merely based on the discussion that the particles of the '415 patent can accept 5-500 femtosecond pulses, is incorrect.

A NET ORIENTATION AT THE INTERFACE IS REQUIRED

Applicants further note that the claimed method requires that the second harmonic-active labels must be hyperpolarizable and contribute to a net orientation at the interface. The Examiner's stated argument is that the particles of the '415 patent can accept pulses between 5 to 500 femtosecond for driving second harmonic generation and thus "would be hyperpolarizable and contribute to a net orientation at the interface". Applicants have explained hereinabove why a particle can be capable of accepting the pulses without being hyperpolarizable. In addition, applicants note that the '415 patent does not teach how to select and align labels to contribute to a net orientation at the (tested) interface. Applicants note that a net orientation does not occur spontaneously based merely on the material used (see right column of page 7752 of Salafsky et al. *id.*).

More importantly, applicants further note that molecules that are second harmonic-active if having a net orientation are not second harmonic-active if randomly oriented (e.g. see left column, last paragraph, of page 7752 of Salafsky et al., re. bulk molecules). Accordingly, without teaching how to select for and align the particles for a net orientation, the '415 patent fails to teach how to practice a method which requires particles to be second harmonic-active labels.

Applicants note that the '415 patent actually states that the particles "can accept pulses ... for ... second harmonic generation". This statement in the '415 patent, when considered in the context of a complete lack of discussion of second harmonic generation, i.e. a complete lack of focus on noncentrosymmetry, hyperpolarizability and net orientation as explained above, must mean that the particles can accept, but not

generate, a second harmonic pulse. For the '415 reference to be enabling of the claimed method it must, but fails, to teach second harmonic-active labels, i.e. the '415 patent fails to even teach the selection of a subset of particles having the requisite properties. Regardless of the lack of requisite selection, a method of employing second harmonic active labels, as opposed to a group of particles of which an unspecific subset might perhaps be employed in that method, is not taught by the '415 patent.

Accordingly, in light of the arguments made above, because The '415 patent does not teach a method that uses second harmonic active labels that are hyperpolarizable and contribute to a net orientation at the interface as recited in the claims, the '415 patent does not anticipate the claimed invention.

Rejections Under 35 U.S.C. §103(a)

On Page 4 of the September 10, 2004 Final Office Action, the Examiner rejected Claims 2, 7, 8, 27 and 28 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Quinn et al. The Examiner alleged that Quinn et al. disclose second harmonic generation and sum-frequency generation techniques utilized with second harmonic labels for detecting molecules of interest. The Examiner further alleged that although the '415 patent do not specifically disclose the use of second harmonic generation as the surface selective technique, it would have been obvious to one of ordinary skill in the art to use a surface selective technique such as taught by Quinn et al. with the second harmonic label of the '415 patent because the '415 patent specifically teach that their labels can be used in second harmonic generation processes (col 13, lines 57-60.)

As previously addressed in a December 2, 2003 telephone conference between Examiner Gary Counts, Supervisory Examiner Long Le and the undersigned, as well as the January 23, 2004 Amendment, and accepted by the Examiner, Applicants' claims recite subject matter that is patentable over Quinn et al. Specifically, applicants' recitation that an unlabeled molecule at the interface would be undetectable using a given surface selective technique clearly distinguishes applicants' claims from Quinn et al. which teaches enhancing a signal already present (i.e. detectable). The '415 Patent in combination with Quinn et al. does not cure this deficiency for the reasons discussed above in reply to the anticipation rejection.

The Examiner rejected Claims 5, 24, and 25 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Mattingly et al., (US 5,145,790).

As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Mattingly et al. as suggested by the Examiner.

The Examiner rejected Claim 9 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Buechler et al. (US 6,194,222).

As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Buechler et al. as suggested by the Examiner.

The Examiner rejected Claims 10, 11, and 35 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Wang et al. (US 5,696,157).

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As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Wang et al. as suggested by the Examiner.

The Examiner rejected Claims 14 and 16 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Eisenthal et al., J. Phys. Chem. 1996, 100(31):12997-13006.

As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Eisenthal et al. as suggested by the Examiner.

The Examiner rejected Claim 15 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Conboy et al., J. Chem. 1994, 98:9688-9692.

As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Conboy et al. as suggested by the Examiner.

The Examiner rejected Claims 17-20 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Eisenthal et al. (US 6,055,051).

As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Eisenthal et al. as suggested by the Examiner.

The Examiner rejected Claim 26 under 35 U.S.C. 103(a) as allegedly unpatentable over the '415 patent in view of Tadano et al. (US 5,962,248).

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As argued hereinabove, the '415 does not teach the claimed method, and this deficiency is not cured by combining reference with Tadano et al. as suggested by the Examiner.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw each of the rejections under 35 U.S.C. §103 over The '415 patent in view of the secondary references.

Examiner's Response to Arguments

The Examiner stated that applicants have argued that the '415 patent does not teach the absolute requirement of non-centrosymmetry for second harmonic generation, but that this feature is not recited in the rejected claims.

In response, applicants note that non-centrosymmetry is an absolute requirement for an entity to be second harmonic-active (see Salafsky et al., *id.*). By requiring in their claims "second harmonic-active label", applicants are necessarily reciting that their labels are noncentrosymmetric.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

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No fee, apart from the closed \$60.00 fee for a one month extension of time, is deemed necessary in connection with the filing of this response. However, if an additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents
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Effects on hyperpolarizabilities of molecular interactions in associating liquid mixtures

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We have measured the second and third order hyperpolarizabilities β and γ using the technique of electric field induced second harmonic generation in a variety of weakly associating (e.g., nitrobenzene-benzene) and strongly associating (e.g., water-methanol) liquid mixtures. These experiments are shown to yield interesting information on dipolar forces, hydrogen bonding, charge transfer interactions, and other solute-solute, solute-solvent effects.

I. INTRODUCTION

The technique of electric field induced second harmonic generation in liquids¹⁻⁴ has proven to be extremely useful in the determination of both the second order β and third order γ hyperpolarizabilities. Extensive measurements¹ on both conjugated and nonconjugated organic molecules have elucidated the crucial role played by the delocalized π -electron contributions to these nonlinearities. As a result of these experiments, the close relationship between β and the donor-acceptor strength of a substituent on a benzene ring is now quantitatively understood.^{5,6} In addition, measurements⁷ using this technique on *ortho*, *meta*, and *para*-nitroaniline in the liquid state have led to a theoretical understanding of the importance of the intramolecular donor-acceptor charge transfer contribution to β . As a further extension of both experiment and theory, actual intermolecular charge transfer complexes (e.g., the classic pyridine-iodine system) have been investigated.⁸

As discussed previously,^{1,2} nonlinear measurements of organic molecules in the liquid phase have many advantages over similar measurements in the gaseous or crystalline state. Namely, many of the most interesting highly conjugated molecules tend to readily decompose at the high temperatures required to vaporize them; however, they can be readily dissolved in an appropriate liquid solvent. Organic crystals, on the other hand, are difficult and time consuming to grow, and data analysis requires the knowledge of the crystal structure which may not have been determined. Another very important reason for studying molecular nonlinearities in the liquid phase is that chemical reactions occur most readily in this phase. Thus, measurements of electric field induced second harmonic generation in liquid mixtures or solutions can provide a means of obtaining information on molecular associations and correlations, intermolecular charge transfer interactions, hydrogen bonding, and dipolar interactions. Most previous work has concentrated on studying pure liquids and not mixtures. However, as we will show, mixtures can give important information on these molecular interactions.

II. LOCAL FIELDS AND MOLECULAR CORRELATIONS

The polarization P_i produced in a molecule by an electric field E_j is given by

$$P_i = \alpha_{ij}E_j + \beta_{ijk}E_jE_k + \gamma_{ijkl}E_jE_kE_l, \quad (1)$$

where the i, j, k, l refer to the molecular coordinate axes and, α_{ij} is the usual linear polarizability of the molecule, β_{ijk} is the second order molecular hyperpolarizability, and γ_{ijkl} is the third order molecular hyperpolarizability. From the above equation we can see that β vanishes by symmetry in a molecule with a center of inversion (e.g., benzene) whereas α and γ do not. Thus, β is particularly sensitive to interactions which remove such a center of symmetry.

The experimental technique of electric field induced second harmonic generation used to accurately determine these hyperpolarizabilities has been discussed in detail elsewhere,¹ and thus we only give a brief summary here. A static field E_0 and a laser field E_ω at frequency ω (polarized along the direction of E_0) applied to a liquid will produce a second harmonic polarization $P_{2\omega}$ at frequency 2ω given by

$$P_{2\omega} = \Gamma E_0 E_\omega^2, \quad (2)$$

where Γ is the macroscopic third order nonlinearity of the liquid. For a pure liquid this macroscopic nonlinearity Γ is related to the microscopic hyperpolarizability γ of a single molecule via

$$\Gamma = N\gamma f_0^2 f_{2\omega}^2, \quad (3)$$

where N is the number of molecules/cm³, and the f 's are the local field factors evaluated at the frequency indicated. Equation (3) is only appropriate for nonassociating liquids. For a polar liquid there are two important contributions to γ , namely^{1,9}

$$\gamma = \gamma_e + \mu\beta/5kT, \quad (4)$$

where γ_e is the purely electronic average third order hyperpolarizability^{1,9} (which does not vanish for centrosymmetric molecules) and where the temperature dependent rotational term is proportional to the dipole moment μ and the vector part of the second order hyperpolarizability^{1,9} $\beta = (\beta_{xxx} + \beta_{xyy} + \beta_{zzz})$, where x is along μ . Since β does vanish in a centrosymmetric molecule (as μ does) it is sensitive (for example) to chemical charge transfer interactions which remove this inversion center. For noninteracting mixtures Eq. (3) can be generalized to¹

$$\Gamma_{mix} = \sum_i (N\gamma_i f_{0i}^2 f_{2\omega i}^2), \quad (5)$$

where the subscript i indicates that each factor in the